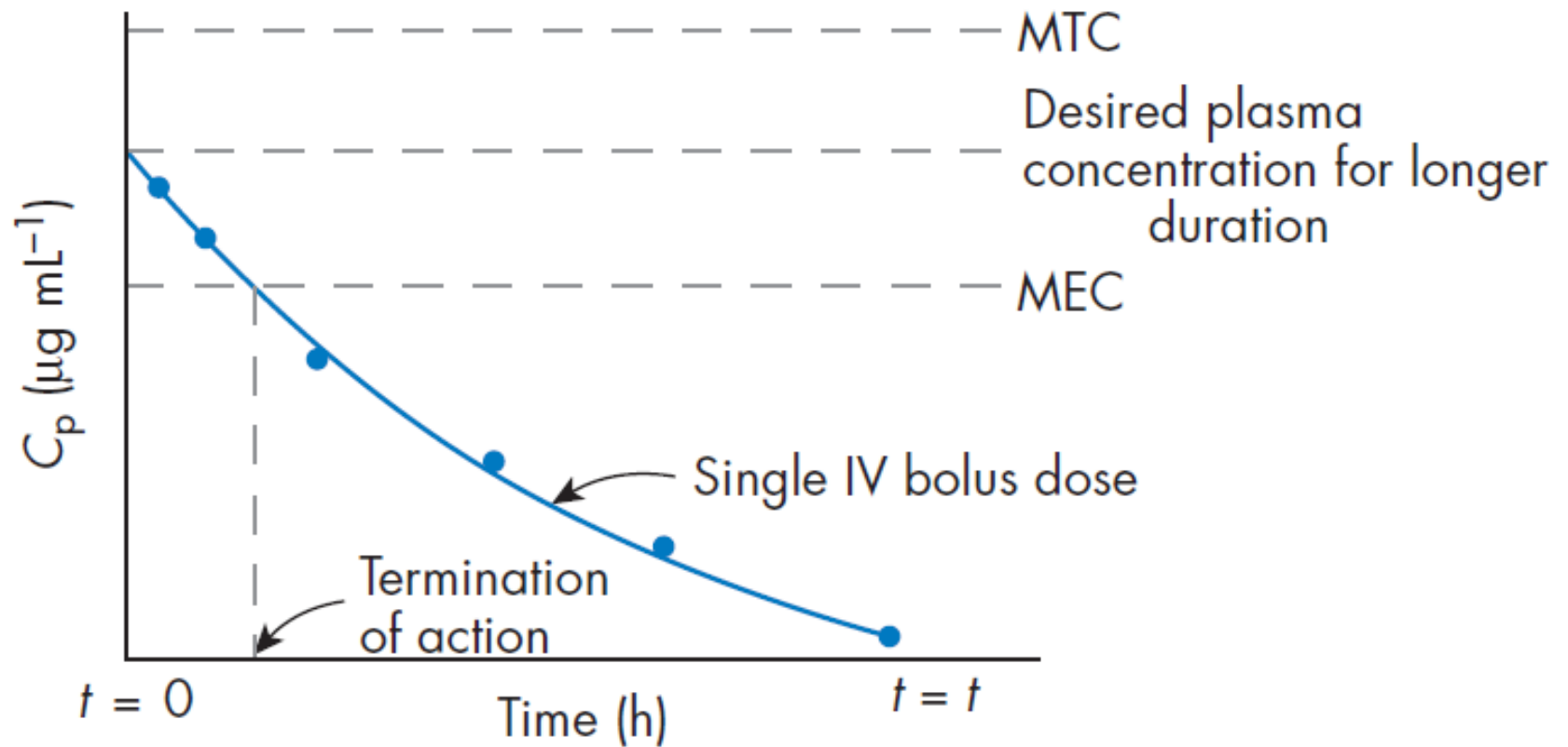


2.6 PK of constant rate infusion

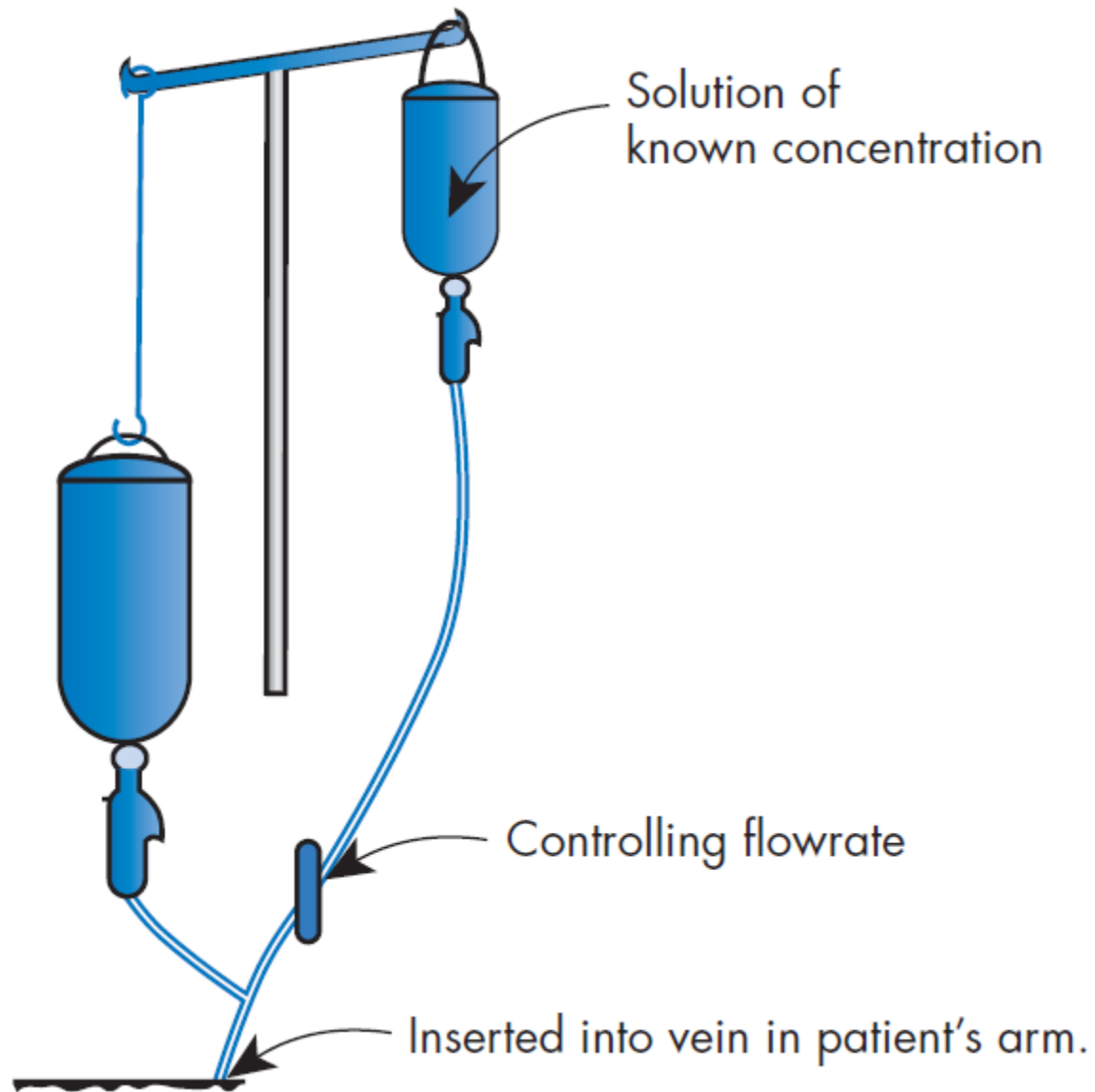


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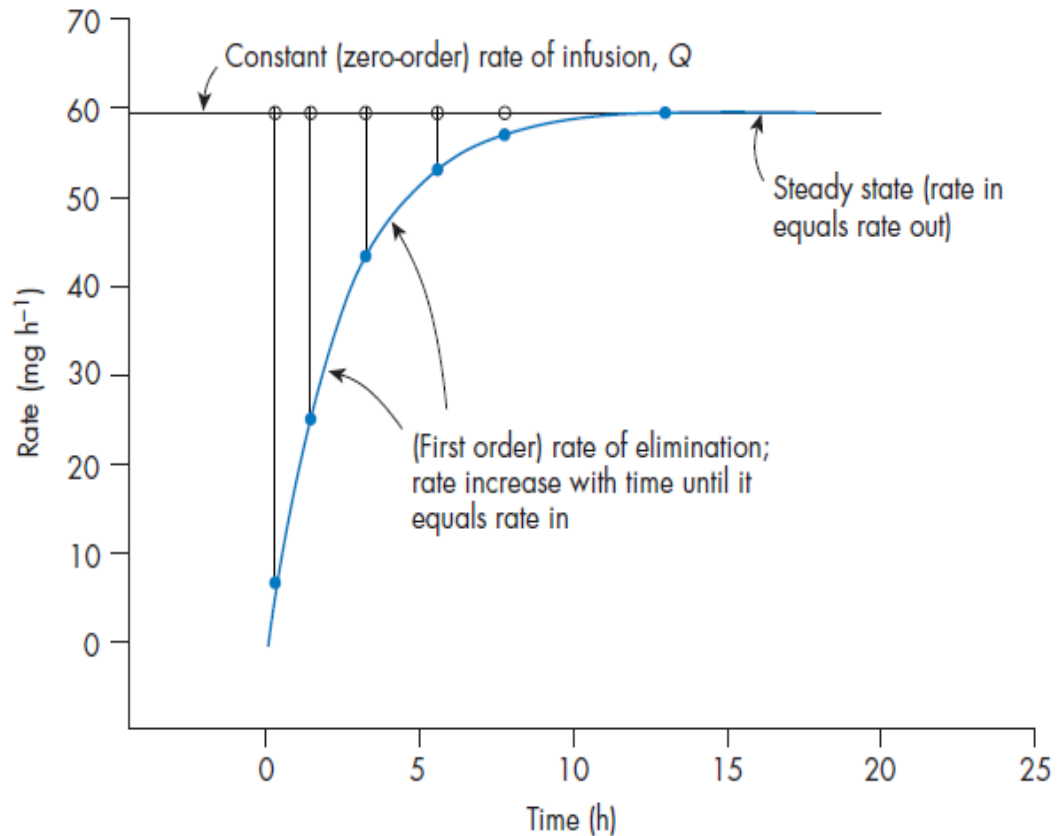




- It is common practice, in the hospital setting to infuse a drug at a constant rate (constant rate input or zero-order input).
- The **infusion rate** of a drug is controlled by:
 - Flow rate
 - Concentration of the drug in solution.



- Initially, the rate at which drug enters the body, though constant, is greater than the rate at which drug is eliminated;
- This allows the drug to reach a certain amount and concentration in the body.





- As time increases, the difference between the rate at which drug enters blood and the rate at which drug leaves blood becomes smaller.
 - This difference becomes zero at time infinity when rate of elimination equals the rate at which the drug is being administered.
 - Hence, there is no change in mass (amount) of drug or plasma concentration of drug with time as long as the chosen constant rate (zero-order) input is maintained.

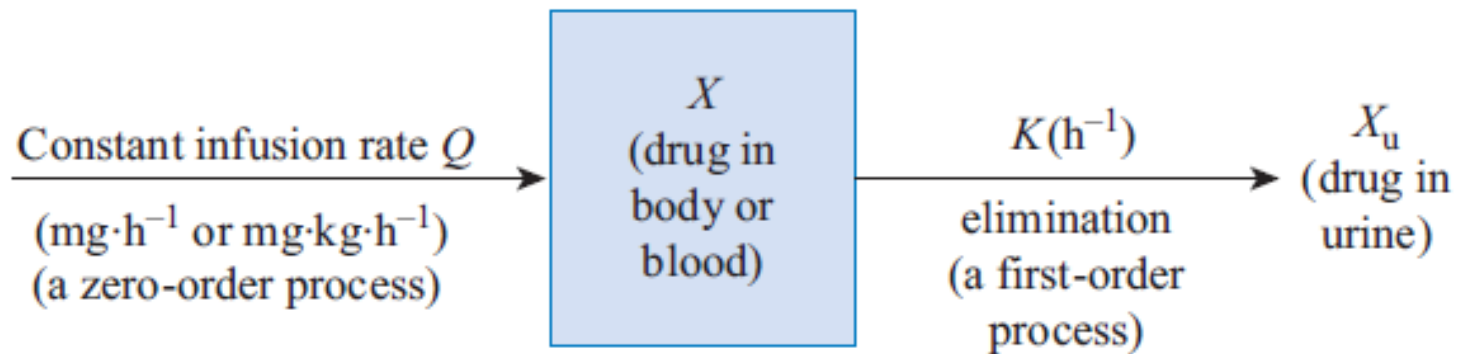


- In the calculation of the different PK parameters, the following simplifying **assumptions** are made:
 1. The drug undergoes no metabolism (i.e. monitoring for unchanged parent drug in the blood)
 2. The drug exhibits the characteristics of a one compartment model (rapid distribution).
 3. The elimination of the drug follows a first order process and passive diffusion.

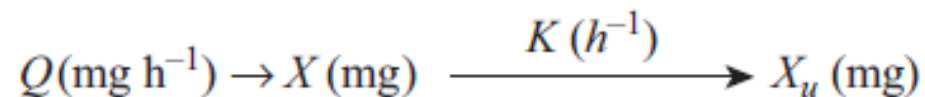


Drug Concentration in the Plasma

SCHEME



SETUP





Steady state concentration

- The change in the amount of drug in the blood/body ($\frac{dX}{dt}$) can be described by:

$$\frac{dX}{dt} = K_o - KX$$

where K_o is the rate of drug infusion, K is elimination rate constant.



- Integration of the above equation gives:

$$X = \frac{K_o}{K} (1 - e^{-Kt})$$

- This can be written in concentration terms:

$$C = \frac{K_o}{VK} (1 - e^{-Kt})$$

- Concentrations in plasma, during infusion, increase according to the above Eqn. but eventually approach a constant value.

■ ■ ■

- At $t \rightarrow \infty$, $e^{-Kt} \rightarrow 0$, and

$$C = \frac{K_o}{VK}$$

- This constant drug concentration or plateau describes a **steady state** situation since at this concentration, the elimination rate equals the infusion rate and $dC/dt = 0$.
- Therefore, the steady-state concentration in plasma C_{ss} is given by:

$$C_{ss} = \frac{K_o}{VK}$$



Systemic clearance

- From the above equation, the $V.K$ term is the systemic clearance ($CL_s = VK$).
- C_{ss} is directly proportional to the infusion rate and inversely proportional to the systemic clearance of the drug.
- The systemic clearance of a drug is readily calculated from the ratio of infusion rate to steady-state drug concentration in plasma:

$$CL_s = VK = \frac{K_o}{C_{ss}}$$



Elimination rate constant (K) and half-life ($t_{1/2}$)

- Substitution for $\frac{K_0}{VK}$ in the equation $C = \frac{K_0}{VK}(1 - e^{-Kt})$

$$C = C_{ss}(1 - e^{-Kt})$$

- Rearranging this equation:

$$\frac{C_{ss} - C}{C_{ss}} = e^{-Kt}$$



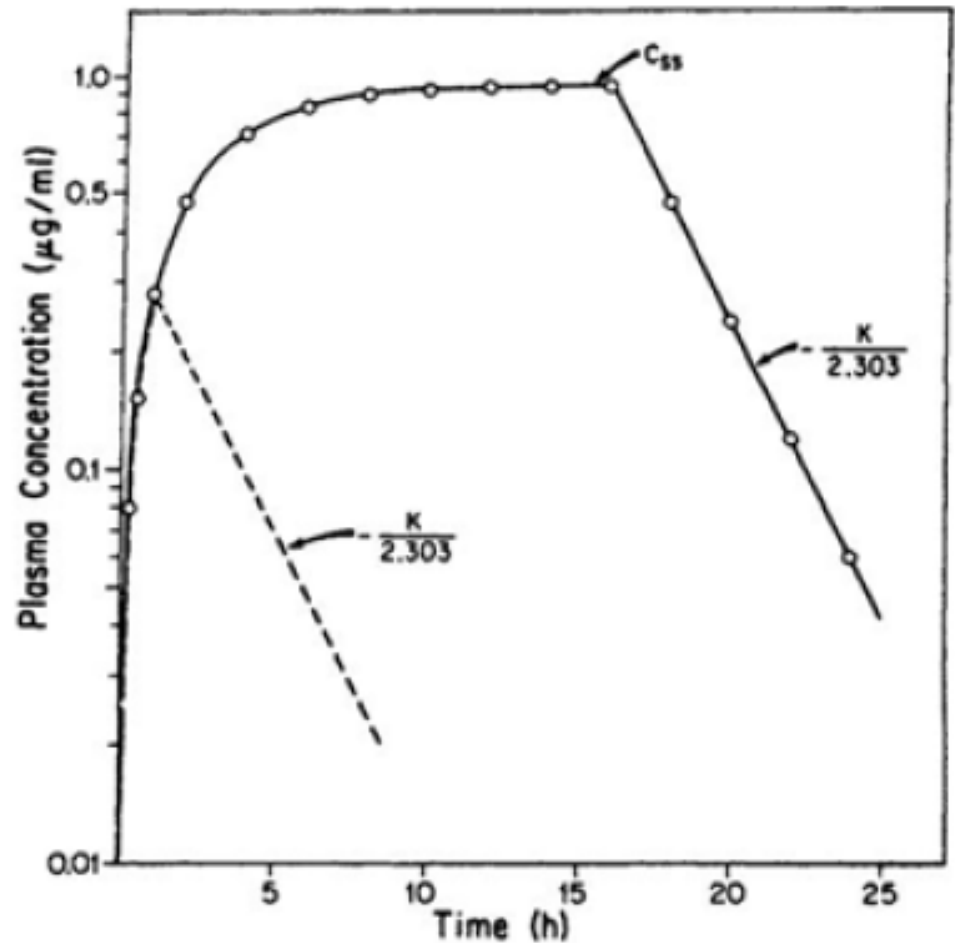
- Therefore,

$$\log \frac{C_{ss} - C}{C_{ss}} = -\frac{Kt}{2.303}$$

- A semi log plot of $\frac{C_{ss}-C}{C_{ss}}$ vs. t yields a straight line with a slope of $-\frac{K}{2.303}$.
- The half-life may be estimated from the relation:

$$t_{1/2} = \frac{0.693}{K}$$

- The elimination rate constant may also be determined using the declining drug concentration in plasma versus time data collected after stopping the infusion.





- Note:
 - If drug concentration versus time data are obtained during as well as after constant rate intravenous infusion, one can calculate systemic clearance CL_s and apparent volume of distribution V from the total area under the concentration versus time curve (AUC) (**read**).



Simultaneous Rapid I.V. Injection and I.V. Infusion

- Since the time required to reach steady state will be very long for a drug with a long half-life, it is often desirable to administer an IV **loading** dose just before starting the intravenous infusion.
- The loading dose should be large enough to yield the desired steady-state drug concentration in plasma immediately upon injection.
- The infusion rate should be fast enough to maintain this concentration.



- The mass of drug in the body at a time from the infusion alone:

$$X = \frac{K_o}{K} (1 - e^{-Kt})$$

- The mass of drug in the body at any time from the intravenous bolus (loading dose).

$$X = X_o e^{-Kt}$$



- If a loading dose is administered at the time an intravenous infusion of the drug is started:

$$(X)_t = \frac{K_o}{K} (1 - e^{-Kt}) + X_o e^{-Kt}$$

where X_o is the loading dose and $(X)_t$ is the total amount of drug in the body at any time from both bolus and infusion.

- This equation can be modified in terms of concentration:

$$(C)_t = \frac{K_o}{VK} (1 - e^{-Kt}) + \frac{X_o}{V} e^{-Kt}$$



- From the relation $C_{ss} = \frac{K_0}{VK}$, substituting for the term $\frac{K_0}{VK}$ in the above equation:

$$(C_p)_t = C_{ss}(1 - e^{-Kt}) + \frac{X_0}{V} e^{-Kt}$$

- Requiring that the total plasma drug concentration from bolus and infusion at time infinity be equal to the total plasma drug concentration from bolus and infusion at time zero:

$$C_{ss}(1 - e^{-K\infty}) + \frac{X_0}{V} e^{-K\infty} = C_{ss}(1 - e^{-K0}) + \frac{X_0}{V} e^{-K0}$$



- Reducing the above equation will give:

$$C_{ss} = \frac{X_o}{V}$$

- Therefore,

$$X_o(\text{Loading dose}) = C_{ss} \cdot V$$

- The loading dose can also be obtained from the relation:

$$C_{ss} = \frac{K_o}{VK}$$



Urinary Excretion Data

- The differential equation for the rate of appearance of unchanged drug in the urine during infusion is the same as that describing urinary excretion of drug following an intravenous bolus injection:

$$\frac{dX_u}{dt} = K_u X$$

- Substituting $X = \frac{K_o}{K} (1 - e^{-Kt})$ and integrating, yields:

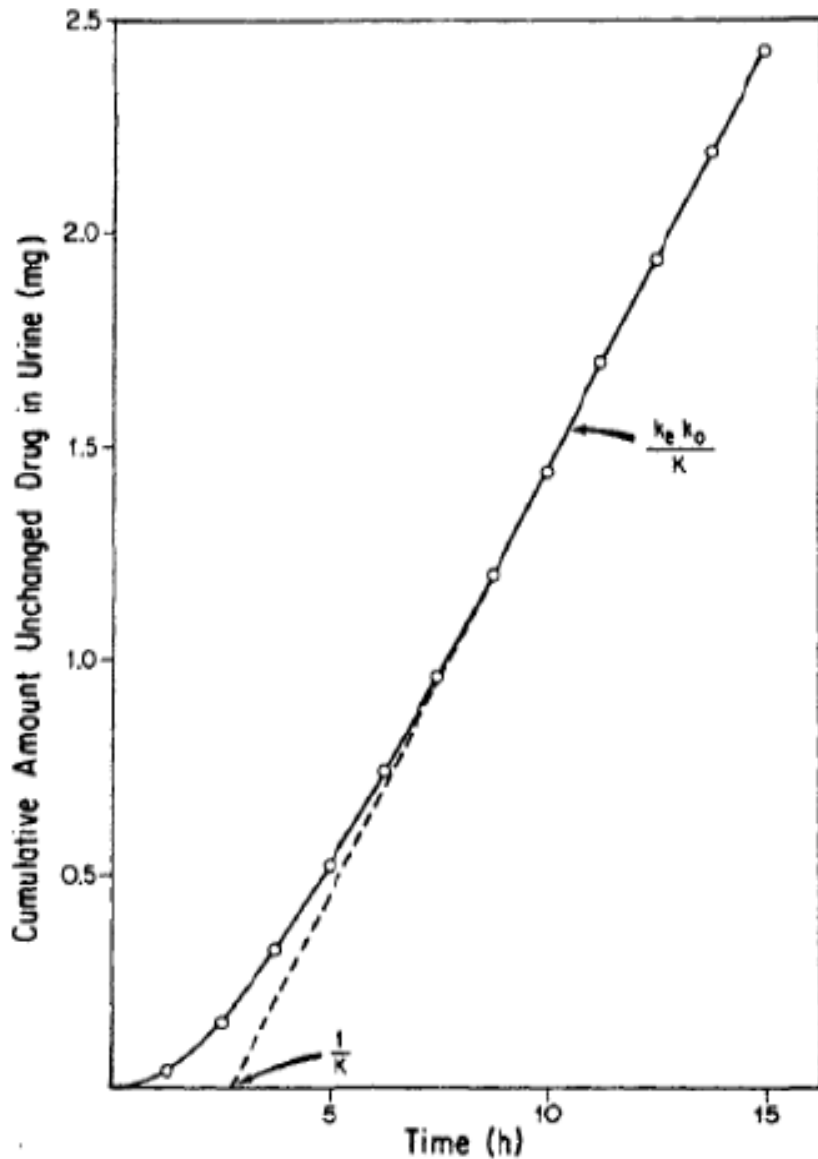
$$X_u = \frac{K_u K_o}{K} t - \frac{K_u K_o}{K^2} (1 - e^{-Kt})$$



- When the drug has been infused for a sufficient period so as to approach steady state in the plasma, the term $e^{-Kt} \rightarrow 0$
- Therefore,

$$X_u = \frac{K_u K_o}{K} t - \frac{K_u K_o}{K^2}$$

- A plot of X_u vs. t is curvilinear initially but eventually becomes linear.



- The slope of the linear region is $\frac{K_u K_0}{K}$
- Extrapolation of the linear segment of the curve to the time axis yields an intercept equal to $1/K$
- Both K and K_u can be estimated.



- Quiz
 - Plot the following graphs (for a drug given intravenously)
 - A. Plasma concentration versus time
 - B. Amount of drug in body versus time
 - C. Amount of drug excreted unchanged versus time